

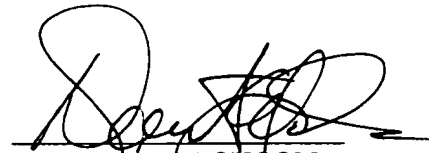
### REMARKS

The specification and claims have been amended to add a Sequence Listing (both paper and computer readable copies) and sequence identifiers were appropriate. No new matter is added by this amendment, and the Examiner is respectfully requested to enter it.

It is respectfully submitted that all claims are in condition for allowance. Early action to that end is respectfully requested. The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning the amendment or specification,

Respectfully submitted,

DATE: 11/7/2001

  
DAVID A. JACKSON  
Attorney for Applicant(s)  
Registration No. 26,742

KLAUBER & JACKSON  
411 Hackensack Avenue  
Hackensack, New Jersey 07601  
(201) 487-5800

### **Marked Up Version Showing Changes Made**

The paragraph at page 3, lines 9-12:

A second aspect of the invention provides methods for diagnosis of Alzheimer's disease that comprise detecting in a sample of CSF the presence or level of at least one Alzheimer's Disease-Associated Protein Isoform (API), e.g., one or more of the APIs disclosed herein or any combination thereof (SEQ ID NOs:1-458).

The paragraph from page 24, line 27 to page 25, line 2:

The first group comprises of APIs that are decreased in the CSF of subjects having Alzheimer's disease as compared with the CSF of subjects free from Alzheimer's disease. The amino acid sequences of peptides produced from these APIs by proteolysis using trypsin and identified by tandem mass spectrometry and database searching using the SEQUEST program are listed in Table IV (SEQ ID NOs:1-269), in addition to their corresponding pIs and MWs. For one API, the partial sequence information derived from tandem mass spectrometry was not found to be described in any known public database. This API is listed as 'NOVEL' in Table IV, and the partial amino acid sequence information derived from manually interpreting the MS/MS spectrum of tryptic peptides of this API as described in the Example infra, is given in Table IX (SEQ ID NOs:463, 466, 469, 472, 475, 478, 481, 484, 487).

Please substitute Table IV at page 25, line 3 to page 31, line 2, with the amended Table IV submitted in the attached pages entitled "Table IV". Table IV is amended to include sequence identifiers.

The paragraph at page 31, lines 3-8:

The second group comprises APIs that are increased in the CSF of subjects having Alzheimer's disease as compared with the CSF of subjects free from Alzheimer's disease. The amino acid sequences of peptides produced from these APIs by proteolysis using trypsin and identified by tandem mass spectrometry and database searching using the

SEQUEST program are listed in Table V (SEQ ID NOs:270-458), in addition to their corresponding pIs and MWs.

Please substitute Table V at page 31, line 10 to page 36, line 1, with the amended Table V submitted in the attached pages entitled "Table V". Table V is amended to include sequence identifiers.

Please substitute Table VI at page 39, lines 1-40, with the amended Table VI submitted in the attached pages entitled "Table VI". Table VI is amended to include sequence identifiers.

Please substitute Table IX at page 62, line 15 to page 63, line 1, with the amended Table IX submitted in the attached pages entitled "Table IX". Table IX is amended to include sequence identifiers.

**In the Claims:**

14. (Amended) A preparation comprising an isolated human protein, said protein comprising a tryptic digest peptide having the following partial sequence as determined by mass spectrometry: PGLGM (SEQ ID NO:467).

15. (Amended) A preparation comprising an isolated human protein, said protein comprising a tryptic digest peptide having the following partial sequence as determined by mass spectroscopy: GPLGM (SEQ ID NO:479).

16. (Amended) A preparation comprising an isolated human protein, said protein comprising a tryptic digest peptide having the following partial sequence as determined by mass spectroscopy: PGLGF (SEQ ID NO:470).

17. (Amended) A preparation comprising an isolated human protein, said protein comprising a tryptic digest peptide having the following partial sequence as determined by mass spectroscopy: GPLGF (SEQ ID NO:482).

18. (Amended) A preparation comprising an isolated human protein, said protein comprising a tryptic digest peptide having the following partial sequence as determined by mass spectrometry: PGIGM (SEQ ID NO:473).

19. (Amended) A preparation comprising an isolated human protein, said protein comprising a tryptic digest peptide having the following partial sequence as determined by mass spectroscopy: GPIGM (SEQ ID NO:485).

20. (Amended) A preparation comprising an isolated human protein, said protein comprising a tryptic digest peptide having the following partial sequence as determined by mass spectroscopy: PGIGF (SEQ ID NO:476).

21. (Amended) A preparation comprising an isolated human protein, said protein comprising a tryptic digest peptide having the following partial sequence as determined by mass spectroscopy: GPIGF (SEQ ID NO:488).

23. (Amended) The preparation according to any one of claims 14, 15, 16, 17, 18, 19, 20 or 21, wherein the protein further comprising a tryptic digest peptide having the following partial sequence as determined by mass spectrometry: HQV (SEQ ID NO:464).

24. (Amended) The preparation according to any one of claims 14, 15, 16, 17, 18, 19, 20 or 21, wherein the protein further comprising a tryptic digest peptide having the following partial sequence as determined by mass spectrometry: HQV (SEQ ID

NO:464), wherein the tryptic digest peptide has a mass of 1096.56 Da, and an N-terminal mass of 0 Da, and a C-terminal mass of 733.50 Da, said masses having an error of measurement of 100 parts-per-million or less.

25. (Amended) A preparation comprising an isolated human protein, said protein comprising a tryptic digest peptide having the following partial sequence as determined by mass spectroscopy: HQV (SEQ ID NO:464).

33. (Amended) An isolated nucleic acid molecule that hybridizes under highly stringent conditions or moderately stringent conditions to the following nucleic acid sequence: CCNCCNYTNGGNATG (SEQ ID NO:469).

34. (Amended) An isolated nucleic acid molecule that hybridizes under highly stringent conditions or moderately stringent conditions to the following nucleic acid sequence: GGNCCNYTNGGNATG (SEQ ID NO:481).

35. (Amended) An isolated nucleic acid molecule that hybridizes under highly stringent conditions or moderately stringent conditions to the following nucleic acid sequence: CCNCCNYTNGGNTTY (SEQ ID NO:472).

36. (Amended) An isolated nucleic acid molecule that hybridizes under highly stringent conditions or moderately stringent conditions to the following nucleic acid sequence: GGNCCNYTNGGNTTY (SEQ ID NO:484).

37. (Amended) An isolated nucleic acid molecule that hybridizes under highly stringent conditions or moderately stringent conditions to the following nucleic acid sequence: CCNGGNATHGGNATG (SEQ ID NO:475).

38. (Amended) An isolated nucleic acid molecule that hybridizes under highly stringent conditions or moderately stringent conditions to the following nucleic acid sequence: CCNGGNATHGGNTTY (SEQ ID NO:478).

39. (Amended) An isolated nucleic acid molecule that hybridizes under highly stringent conditions or moderately stringent conditions to the following nucleic acid sequence: GGCCNATHGGNATG (SEQ ID NO:487).

40. (Amended) An isolated nucleic acid molecule that hybridizes under highly stringent conditions or moderately stringent conditions to the following nucleic acid sequence: GGCCNATHGGNTTY (SEQ ID NO:489).

41. (Amended) The isolated nucleic acid molecule according to any one of claims 33, 34, 35, 36, 37, 38, 39, or 40, wherein the nucleic acid also hybridizes under highly stringent conditions or moderately stringent conditions to the following nucleic acid sequence: CAYCARGTN (SEQ ID NO:466).

42. (Amended) An isolated nucleic acid molecule that hybridizes under highly stringent conditions or moderately stringent conditions to the following nucleic acid sequence: CCCGGCCTGGGCATG (SEQ ID NO:468).

43. (Amended) An isolated nucleic acid molecule that hybridizes under highly stringent conditions or moderately stringent conditions to the following nucleic acid

sequence: GGCCCCCTGGGCATG (SEQ ID NO:480).

44. (Amended) An isolated nucleic acid molecule that hybridizes under highly stringent conditions or moderately stringent conditions to the following nucleic acid sequence: CCCGGCCTGGGCTTC (SEQ ID NO:471).

45. (Amended) An isolated nucleic acid molecule that hybridizes under highly stringent conditions or moderately stringent conditions to the following nucleic acid sequence: GGCCCCCTGGGCTTC (SEQ ID NO:483).

46. (Amended) An isolated nucleic acid molecule that hybridizes under highly stringent conditions or moderately stringent conditions to the following nucleic acid sequence: CCCGGCATCGGCATG (SEQ ID NO:474).

47. (Amended) An isolated nucleic acid molecule that hybridizes under highly stringent conditions or moderately stringent conditions to the following nucleic acid sequence: CCCGGCATCGGCTTC (SEQ ID NO:477).

48. (Amended) An isolated nucleic acid molecule that hybridizes under highly stringent conditions or moderately stringent conditions to the following nucleic acid sequence: GGCCCCATCGGCATG (SEQ ID NO:491).

49. (Amended) An isolated nucleic acid molecule that hybridizes under highly stringent conditions or moderately stringent conditions to the following nucleic acid sequence: GGCCCCATCGGCTTC (SEQ ID NO:492).

50. (Amended) The isolated nucleic acid molecule according to any one of claims 42, 43, 44, 45, 46, 47, 48 or 49, wherein the nucleic acid also hybridizes under highly stringent conditions or moderately stringent conditions to the following nucleic acid sequence: CACCAGGTG (SEQ ID NO:465)





Table IV. APIs Decreased in CSF of Subjects Having Alzheimer's disease

| AF#   | API#    | Amino Acid Sequences of Tryptic Digest Peptides                  | SEQ ID NO:           | pI   | MW(Da) |
|-------|---------|--|----------------------|------|--------|
| AF-1  | API-47  | EDYICYAR,<br>GKPPPSFSWTR,<br>QPEYAVVQR                           | 1<br>2<br>3          | 4.79 | 150081 |
| AF-1  | API-242 | IIMLFDTGGEER,<br>FVVTDDGQTR                                      | 4<br>5               | 4.79 | 150081 |
| AF-2  | API-1   | SGELEQEEER,<br>EEEEEMAVVPQGLFR                                   | 6<br>7               | 4.28 | 21349  |
| AF-3  | API-48  | LVNIYDSMPLR,<br>VIVVWNNIGEK,<br>YLELFQR                          | 8<br>9<br>10         | 8.10 | 34846  |
| AF-5  | API-49  | DCSGVSLHLTR  | 11                   | 7.34 | 36554  |
| AF-6  | API-2   | TEAYLEAIR  | 12                   | 4.91 | 29812  |
| AF-8  | API-194 | DGNPFYFTDHR  | 13                   | 4.93 | 187927 |
| AF-9  | API-3   | AETYEGVYQCTAR  | 14                   | 5.21 | 136768 |
| AF-10 | API-50  | FWDYLR,<br>GEVQAMLGQSTEELR<br>KVEQAVETEPEPELR<br>SELEEQLTPVAEETR | 15<br>16<br>17<br>18 | 5.19 | 17694  |
| AF-10 | API-51  | VNSDGGGLVALR   | 19                   | 5.19 | 17694  |
| AF-13 | API-4   | HYDGSYSTFGER,<br>VGFYESDVMGR,<br>LPPNVVEESAR                     | 20<br>21<br>22       | 6.01 | 184530 |
| AF-14 | API-52  | ADLSGITGAR,<br>EIGELYLPK   | 23<br>24             | 4.72 | 63166  |
| AF-14 | API-243 | FEDGVLDPDYPR   | 25                   | 4.72 | 63166  |
| AF-15 | API-53  | ELDESLQVAER  | 26                   | 4.47 | 38970  |
| AF-15 | API-244 | TEVQLEHLR  | 27                   | 4.47 | 38970  |
| AF-16 | API-54  | EGPVLILGR  | 28                   | 5.19 | 46876  |
| AF-17 | API-5   | EPGEFALLR,<br>TALASGGVLDASGDYR,<br>YEAAVPDPR,<br>VAMHLVCPSR      | 29<br>30<br>31<br>32 | 5.82 | 50294  |
| AF-18 | API-55  | IVIGMDVAASEFYR,<br>LGAEVYHTLK                                    | 33<br>34             | 4.87 | 49219  |
| AF-18 | API-245 | VEQATQAIPMER   | 35                   | 4.87 | 49219  |
| AF-21 | API-6   | LSPYVNYSFR,<br>AETYEGVYQCTAR,<br>GKPPPSFSWTR,<br>IDGDTIIFSNVQER  | 36<br>37<br>38<br>39 | 5.40 | 141094 |

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| AF#   | API#    | Amino Acid Sequences of Tryptic Digest Peptides                                   | SEQ ID NO:                 | pI   | MW(Da) |
|-------|---------|---|----------------------------|------|--------|
| AF-22 | API-56  | EGLDLQVLEDSGR,<br>LICSELNGR,<br>RTMRDQDTGK  | 40<br>41<br>42             | 4.93 | 133773 |
| AF-22 | API-57  | YIFHNFMER,<br>SPEQQETVLDGNLIIR,<br>NGIDIYSLTVDSR,<br>ILDDLSPR                     | 43<br>44<br>45<br>46       | 4.93 | 133773 |
| AF-23 | API-7   | IPTTFENGR   | 47                         | 4.50 | 32473  |
| AF-23 | API-8   | EDEEEEEGENYQK,<br>GEAGAPGEEDIQGPTK,<br>HLEEPGETQNAFLNER                           | 48<br>49<br>50             | 4.50 | 32473  |
| AF-24 | API-9   | EGPVLILGR,<br>IVQFSPSGK,<br>NNLVIFHR  | 51<br>52<br>53             | 5.31 | 46663  |
| AF-25 | API-10  | ASSIIDELFQDR  | 54                         | 5.68 | 36700  |
| AF-26 | API-14  | TMLLQPAGSLGSSYSYR,<br>APEAQVSVQPNFQQDK  | 55<br>56                   | 8.11 | 32305  |
| AF-27 | API-15  | WLQGSQELPR  | 57                         | 5.33 | 141371 |
| AF-27 | API-58  | LSPYVNYSFR,<br>AETYEGVYQCTAR,<br>GKPPPSFSWTR,<br>IDGDTIIFSNVQER,<br>NALGAIHHTISVR | 58<br>59<br>60<br>61<br>62 | 5.33 | 141371 |
| AF-28 | API-16  | IALVITDGR   | 63                         | 5.13 | 158568 |
| AF-28 | API-59  | ALYLQYTDETFR,<br>QSEDSTFYLGER,<br>GAYPLSIEPIGVR                                   | 64<br>65<br>66             | 5.13 | 158568 |
| AF-29 | API-196 | LVGGPMDASVEEEGVR<br>ALDFAVGEYNK   | 67                         | 9.22 | 47059  |
| AF-30 | API-17  | LAAAVSNFGYDLR,<br>TSLEDFYLDEER  | 68<br>69                   | 5.67 | 48057  |
| AF-31 | API-60  | YIETDPANR,<br>AGALNSNDAFVLK,<br>HVVPNEVVVQR                                       | 70<br>71<br>72             | 6.07 | 91258  |
| AF-32 | API-18  | EPGEFALLR,<br>TALASGGVLDASGDYR,<br>VAMHLVCPSR                                     | 73<br>74<br>75             | 6.17 | 48958  |
| AF-34 | API-61  | TGLEAISNHK,<br>FFEECDPNK  | 76<br>77                   | 4.54 | 145408 |
| AF-35 | API-62  | QQTEWQSGQR,<br>SELEEQLTPVAEETR  | 78<br>79                   | 5.21 | 18623  |
| AF-37 | API-19  | DVIATDKEDVAFK,  | 80                         | 6.91 | 33523  |

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API

| AF#   | API#    | Amino Acid Sequences of<br>Tryptic Digest Peptides                      | SEQ ID<br>NO:              | pI   | MW(Da) |
|-------|---------|---|----------------------------|------|--------|
|       |         | ENFSCLTR,<br>FVEGLPINDFSR,<br>EVGVYEALK                                 | 81<br>82<br>83             |      |        |
| AF-38 | API-63  | LSELIQPLPLER,<br>LVHGGPCDK,<br>EKPGVYTNVCR,<br>YTNWIQK                  | 84<br>85<br>86<br>87       | 6.47 | 29535  |
| AF-39 | API-64  | CSVFYGA PSK   | 88                         | 7.50 | 35510  |
| AF-39 | API-65  | LVNIYDSMPLR,<br>YLELFQR   | 89<br>90                   | 7.50 | 35510  |
| AF-40 | API-20  | ITWSNPPAQGAR,<br>VGGVQSLGGTGALR,<br>IGADFLAR,<br>NFGLYNER,<br>HIYLLPSGR | 91<br>92<br>93<br>94<br>95 | 7.29 | 38617  |
| AF-41 | API-22  | LEGEACGVYTPR  | 96                         | 5.85 | 17345  |
| AF-42 | API-66  | LIVHNGYCDGR   | 97                         | 5.04 | 18662  |
| AF-43 | API-67  | LGPLVEQGR,<br>LEEQAQQIR   | 98<br>99                   | 9.83 | 14065  |
| AF-43 | API-68  | LVGGPMDASVEEEGVR  | 100                        | 9.83 | 14065  |
| AF-44 | API-69  | EELLPAQDIK  | 101                        | 6.63 | 102328 |
| AF-44 | API-70  | GCPTEEGCGER,<br>AASGTQNNVLR   | 102<br>103                 | 6.63 | 102328 |
| AF-45 | API-23  | ALYYDLISSPDHGTYK,<br>ELLDTVTAPQK,<br>LAAAVSNFGYDLR,<br>TSLEDFYLD EER    | 104<br>105<br>106<br>107   | 6.04 | 46998  |
| AF-46 | API-24  | THPHFVIPYR  | 108                        | 4.71 | 19802  |
| AF-46 | API-197 | QSLEASLAETEGR,<br>YENEVALR  | 109<br>110                 | 4.71 | 19802  |
| AF-46 | API-198 | YEELQQTAGR  | 111                        | 4.71 | 19802  |
| AF-47 | API-25  | EPGEFALLR,<br>TALASGGVLDASGDYR,<br>YEAAVPDPR,<br>VAMHLVCPSR             | 112<br>113<br>114<br>115   | 5.99 | 49664  |
| AF-48 | API-71  | YLELESSGHR,<br>AFLFQESPR  | 116<br>117                 | 5.32 | 122332 |
| AF-49 | API-26  | GLVSWGNI PCGSK,<br>EKPGVYTNVCR<br>DSCQGDSGGPLVCGDHLR                    | 118<br>119                 | 6.94 | 27576  |
| AF-49 | API-27  | TMLLQPAGSLGSSYSYR   | 120                        | 6.94 | 27576  |

| AF#   | API#    | Amino Acid Sequences of Tryptic Digest Peptides   | SEQ ID NO:  | pI   | MW(Da) |
|-------|---------|---|---|------|--------|
| AF-50 | API-72  | NVPLPVIAELPPK   | 121   | 6.82 | 71337  |
| AF-50 | API-73  | CFEPQLLR,<br>EQPPSLTR   | 122<br>123  | 6.82 | 71337  |
| AF-50 | API-199 | YWNDCEPPDSR,<br>DSPVLIDFFEDTER,<br>GGEGTGYFVDFSVR   | 124<br>125<br>126   | 6.82 | 71337  |
| AF-50 | API-200 | VYLFDFPEGK,<br>CISYSSER   | 127<br>128  | 6.82 | 71337  |
| AF-51 | API-28  | ASSIIDELFQDR  | 129   | 5.70 | 34388  |
| AF-51 | API-30  | SADTLWDIQK,<br>LKDDEVAQLK,<br>LIAPVAEEEEATVPNNK   | 130<br>131<br>132   | 5.70 | 34388  |
| AF-76 | API-86  | EGPVLILGR,<br>NNLVIFHR  | 133<br>134  | 5.59 | 45537  |
| AF-79 | API-201 | LPPNVVEESAR   | 135   | 5.52 | 142378 |
| AF-81 | API-88  | LVESGGGLVQPGGSLR  | 136   | 5.43 | 78299  |
| AF-81 | API-202 | GEASVCVEDWESGDR,<br>VSSQNIQDFPSVLR  | 137<br>138  | 5.43 | 78299  |
| AF-82 | API-89  | LLEACTFHSAK,<br>HSTVLENLPDK   | 139<br>140  | 6.69 | 74838  |
| AF-83 | API-90  | DQYELLCR,<br>QMDFELLQNGAR,<br>IECVSAENTEDCIAK,<br>SPDFQLFSSSHGK,<br>GSNFQWNQLQGK,<br>CGLVPVLAENYK,<br>WCTISNQEANK,<br>FDQFFGEGCAPGSQR,<br>EPVDNAENCHLAR,<br>WCAIGHEETQK,<br>HSTVLENLPDK | 141<br>142<br>143<br>144<br>145<br>146<br>147<br>148<br>149<br>150<br>151 | 6.81 | 71920  |
| AF-84 | API-91  | DNPQTHYYAVAVVK,<br>DQYELLCR,<br>QMDFELLQNGAR,<br>VTCVAEELLK,<br>WCTISNQEANK,<br>EPVDNAENCHLAR,<br>FDQFFGEGCAPGSQR,<br>HSTVLENLPDK   | 152<br>153<br>154<br>155<br>156<br>157<br>158<br>159                      | 6.94 | 73402  |
| AF-85 | API-92  | IPIEDGSGEVVLSR  | 160   | 7.10 | 73878  |
| AF-85 | API-93  | DQYELLCR,<br>FDQFFGEGCAPGSQR,   | 161<br>162  | 7.10 | 73878  |

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| AF#    | API#               | Amino Acid Sequences of<br>Tryptic Digest Peptides  | SEQ ID<br>NO:                          | pI   | MW(Da) |
|--------|--------------------|---|--|------|--------|
|        |                    | SPDFQLFSSSHGK,<br>EPVDNAENCHLAR,<br>CGLVPVLAENYK,<br>HSTVLENLPDK                                | 163<br>164<br>165<br>166               |      |        |
| AF-87  | API-95             | ECCHGDLLECADDR,<br>IYEATLEDCCAK,<br>LGEYGFQNALIVR,<br>DVFLGTFLYEYSR,<br>FQPLVDEPK               | 167<br>168<br>169<br>170<br>171        | 5.95 | 64179  |
| AF-89  | API-97             | GYTQQLAFR,<br>AGDFLEANMYMNLQR   | 172<br>173                             | 5.39 | 65155  |
| AF-90  | API-98             | LPLEYSYGEYR   | 174                                    | 7.61 | 62945  |
| AF-91  | API-99             | LFEELVR,<br>DPVQEAWAEDVDLR,<br>GIFPVLCK,<br>GDYPLEAVR   | 175<br>176<br>177<br>178               | 8.16 | 56352  |
| AF-100 | API-101            | LSCAEDYLSLVLR,<br>LGEYGFQNALIVR,<br>YICENQDTISTK,<br>CCTESLVNR,<br>DVFLGTFLYEYSR,<br>HPDYSVSLLR | 179<br>180<br>181<br>182<br>183<br>184 | 6.08 | 44068  |
| AF-103 | API-102            | INHGILYDEEK,<br>EIMENYNIALR,<br>ITCTEEGWSPTPK   | 185<br>186<br>187                      | 5.93 | 42722  |
| AF-104 | API-103            | YVMLPVADQEK   | 188                                    | 5.09 | 42184  |
| AF-105 | API-104            | GSPAINVAVHVFR   | 189                                    | 5.19 | 42184  |
| AF-107 | API-107            | ITVVDALHEIPVK,<br>DNLAIQTR  | 190<br>191                             | 7.26 | 33226  |
| AF-107 | API-210            | KLVVENVDVLTQMR  | 192                                    | 7.26 | 33226  |
| AF-108 | API-108            | GYCAPGMECVK,<br>GTCEQGPSIVTPPK,<br>AGAAAGGPGVSGVCVK   | 193<br>194<br>195                      | 7.54 | 33136  |
| AF-114 | API-111<br>API-112 | See Table IX  |  | 6.80 | 18741  |
| AF-117 | API-113            | KVEQAVETEPEPELR,<br>SELEEQLTPVAETR  | 196<br>197                             | 4.65 | 13983  |
| AF-119 | API-114            | GTFATLSELHCDK,<br>VVAGVANALAHK,<br>LLVVYPWTQR   | 198<br>199<br>200                      | 7.23 | 11699  |
| AF-149 | API-214            | VEEVKPLEGR  | 201                                    | 4.82 | 190721 |
| AF-150 | API-144            | GPPGPPGGVVVR,   | 202                                    | 6.87 | 157592 |

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AF-14

| AF#    | API#    | Amino Acid Sequences of Tryptic Digest Peptides                                   | SEQ ID NO:                      | pI   | MW(Da) |
|--------|---------|---|---------------------------------|------|--------|
|        |         | VEVLAGDLR   | 203                             |      |        |
| AF-152 | API-146 | FTFEYSR,<br>FTDSENVQER  | 204<br>205                      | 5.04 | 81703  |
| AF-152 | API-147 | VIALINDQR   | 206                             | 5.04 | 81703  |
| AF-152 | API-148 | TATSEYQTFFNPR,<br>ELLESYIDGR  | 207<br>208                      | 5.04 | 81703  |
| AF-154 | API-150 | QEDDLANINQWVK,<br>LCQDLGPGAFR   | 209<br>210                      | 5.03 | 67307  |
| AF-154 | API-151 | DVVLTTTFVDDIK,<br>AIEDYINEFSVR  | 211<br>212                      | 5.03 | 67307  |
| AF-154 | API-152 | WLQGSQELPR  | 213                             | 5.03 | 67307  |
| AF-155 | API-215 | LVGGPMDASVEEEGVR,<br>ALDFAVGEYNK  | 214<br>215                      | 9.21 | 64021  |
| AF-156 | API-153 | DQDGEILLPR  | 216                             | 4.36 | 58083  |
| AF-159 | API-158 | TSLEDFYLDEER  | 217                             | 5.08 | 52008  |
| AF-159 | API-159 | EPGEFALLR,<br>TALASGGVLDASGDYR  | 218<br>219                      | 5.08 | 52008  |
| AF-159 | API-160 | YYTVFDR,<br>QVFGEATK  | 220<br>221                      | 5.08 | 52008  |
| AF-163 | API-165 | IPTTFENGR,<br>CPNPPVQENFDVVK,<br>NILTSNNIDVK,<br>NPNLPPETVDSLK                    | 222<br>223<br>224<br>225        | 4.45 | 34879  |
| AF-163 | API-166 | GEAGAPGEEDIQGPTK  | 226                             | 4.45 | 34879  |
| AF-164 | API-167 | ELDESLQVAER,<br>FMETVAEK,<br>EILSVDCSTNNPSQAK                                     | 227<br>228<br>229               | 5.00 | 33485  |
| AF-169 | API-173 | LGQYASPTAK,<br>GSFEFPVGDAVSK,<br>EELVYELNPLDHR                                    | 230<br>231<br>232               | 8.00 | 34362  |
| AF-170 | API-174 | ELDESLQVAER   | 233                             | 5.41 | 31886  |
| AF-170 | API-175 | GSPAINVAVHVFR,<br>AADDTWEPFASGK   | 234<br>235                      | 5.41 | 31886  |
| AF-170 | API-176 | SWFEPLVEDMQR,<br>LGADMEDVCGR,<br>LEEQAQQIR,<br>SELEEQLTPVAEETR,<br>AATVGSLAQPLQER | 236<br>237<br>238<br>239<br>240 | 5.41 | 31886  |
| AF-172 | API-179 | GPCWCVDR,<br>HLDSVLQQLQTEVYR  | 241<br>242                      | 6.71 | 28747  |
| AF-172 | API-180 | KPNLQVFLGK,   | 243                             | 6.71 | 28747  |

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| AF#    | API#    | Amino Acid Sequences of<br>Tryptic Digest Peptides           | SEQ ID<br>NO:     | pI    | MW(Da) |
|--------|---------|--|-------------------|-------|--------|
|        |         | GLVSWGNIPCGSK,<br>EKPGVYTNVCR,<br>DSCQGDSGGPLVCGDHLR         | 244<br>245<br>246 |       |        |
| AF-173 | API-181 | SNLDEDIIAEENIVSR,<br>NEQVEIR                                 | 247<br>248        | 7.67  | 27476  |
| AF-174 | API-182 | SVTEQGAELSNEER   | 249               | 4.67  | 27811  |
| AF-175 | API-183 | APEAQVSVQPNFQQDK,<br>TMLLQPAGSLGSSYSYR,<br>AQGFTEDTIVFLPQTDK | 250<br>251<br>252 | 5.33  | 24936  |
| AF-176 | API-184 | TMLLQPAGSLGSSYSYR,<br>AQGFTEDTIVFLPQTDK                      | 253<br>254        | 4.86  | 22248  |
| AF-178 | API-185 | LPFVINDGK  | 255               | 6.03  | 22247  |
| AF-178 | API-217 | TMLLQPAGSLGSSYSYR,<br>AQGFTEDTIVFLPQTDK,<br>APEAQVSVQPNFQQDK | 256<br>257<br>258 | 6.03  | 22247  |
| AF-178 | API-219 | TQGFTEDAIVFLPQTDK  | 259               | 6.03  | 22247  |
| AF-181 | API-187 | HVGDLGNVTADK,<br>GDGPVQGIINFEQK                              | 260<br>261        | 5.72  | 16336  |
| AF-183 | API-189 | LVGGPMDASVEEEGVR,<br>ALDFAVGEYNK                             | 262<br>263        | 10.36 | 11160  |
| AF-184 | API-190 | ELLDTVTAPQK,<br>TSLEDFYLDEER                                 | 264<br>265        | 5.31  | 48769  |
| AF-186 | API-238 | IPTTFENGR  | 266               | 4.71  | 29693  |
| AF-187 | API-239 | QPEYAVVQR  | 267               | 4.93  | 154156 |
| AF-190 | API-240 | ELDVLQGR, NNYMYAR  | 268,269           | 5.29  | 29663  |

Table V. APIs Increased In CSF of Subjects Having Alzheimer's Disease

| AF#   | API#    | Amino Acid Sequences of<br>Tryptic Digest Peptides             | SEQ ID<br>NO:            | pI    | MW (Da) |
|-------|---------|--|--------------------------|-------|---------|
| AF-52 | API-74  | GLQDEDGYR,<br>FACYYP   | 270<br>271               | 6.30  | 32573   |
| AF-53 | API-33  | AVMDDFAAFVEK,<br>YICENQDSISSK                                  | 272<br>273               | 5.84  | 45302   |
| AF-54 | API-221 | SELEEQLTPVAEETR  | 274                      | 5.12  | 17520   |
| AF-55 | API-34  | LVGGPMDASVEEEGVR,<br>ALDFAVGEYNK                               | 275<br>276               | 8.10  | 12361   |
| AF-56 | API-75  | NYCGLPGEYWLGNDK,<br>IRPFFPQQ,<br>LESDVSAQMEYCR,<br>DNDGWLTSDPR | 277<br>278<br>279<br>280 | 8.56  | 52128   |
| AF-56 | API-246 | AGALNSNDAFVLK,<br>TGAQELLR                                     | 281<br>282               | 8.56  | 52128   |
| AF-57 | API-35  | MTLDDFR  | 283                      | 6.30  | 68549   |
| AF-57 | API-76  | VFLDCCNYITELR  | 284                      | 6.30  | 68549   |
| AF-57 | API-222 | QSLEASLAETGR   | 285                      | 6.30  | 68549   |
| AF-58 | API-77  | KVEQAVETEPEPELR  | 286                      | 5.01  | 14507   |
| AF-59 | API-36  | TSLEDFYLDEER   | 287                      | 6.74  | 33401   |
| AF-60 | API-37  | GEVQAMLGQSTEELR,<br>KVEQAVETEPEPELR,<br>SELEEQLTPVAEETR,       | 288<br>289<br>290        | 5.39  | 33873   |
| AF-61 | API-78  | QELSEAEQATR,<br>TIYTPGSTVLRY,<br>IPIEDGSGEVLSR                 | 291<br>292<br>293        | 6.76  | 54345   |
| AF-62 | API-38  | GLQDEDGYR,<br>ITQVLHFTK,<br>FACYYP                             | 294<br>295<br>296        | 6.60  | 31004   |
| AF-63 | API-79  | IWDVVEK,<br>QPVPGQQMTLK,<br>EVVADSVWVDVK,<br>DSCVGSLLVK        | 297<br>298<br>299<br>300 | 5.97  | 14897   |
| AF-64 | API-80  | DFDFVPPVVR,<br>SNLDEDIAEENIVSR,<br>IPIEDGSGEVLSR               | 301<br>302<br>303        | 6.67  | 68119   |
| AF-65 | API-81  | CLVNLIEK,<br>FLCTGGVSPYADPNTCR                                 | 304<br>305               | 7.19  | 58620   |
| AF-65 | API-223 | VGDTLNLLNR   | 306                      | 7.19  | 58620   |
| AF-66 | API-82  | VFLDCCNYITELR,<br>FISLGEACK                                    | 307<br>308               | 10.05 | 30092   |
| AF-66 | API-83  | LVGGPMDASVEEEGVR,  | 309                      | 10.05 | 30092   |



| AF#    | API#    | Amino Acid Sequences of<br>Trypic Digest Peptides  | SEQ ID<br>NO:                                 | pI   | MW (Da) |
|--------|---------|--|---|------|---------|
|        |         | ALDFAVGEYNK  | 310   |      |         |
| AF-67  | API-39  | AADDTWEPFASGK  | 311   | 5.02 | 13735   |
| AF-68  | API-84  | LISWYDNEFGYSNR,<br>VPTANVSVDLTCR,  | 312<br>313                                    | 9.06 | 35351   |
| AF-68  | API-85  | ISYQSSSTEER  | 314   | 9.06 | 35351   |
| AF-69  | API-40  | TQVNTQAEQLR,<br>ALVQQMEQLR   | 315<br>316                                    | 5.01 | 46760   |
| AF-69  | API-247 | VLSLAQEQVGGSPEK,<br>AEMADQAAAWLTR,<br>QGSFQGGFR  | 317<br>318<br>319                             | 5.01 | 46760   |
| AF-70  | API-41  | LVMGIPTFGR,<br>EGDGSCFPDALDR,<br>FSNTDYAVGYMLR,<br>GNQWVGYYDDQESVK,<br>QHFTTLIK                            | 320<br>321<br>322<br>323<br>324               | 8.91 | 38789   |
| AF-70  | API-224 | DAIPEDLPPLTADFAEDK,<br>YLYEIAR   | 325<br>326                                    | 8.91 | 38789   |
| AF-71  | API-42  | VFLDCCNYITELR,<br>SNLDEDIAEENIVSR,<br>GYTQQLAFR  | 327<br>328<br>329                             | 6.44 | 68579   |
| AF-72  | API-43  | IDQTVEELR,<br>TQVNTQAEQLR,<br>ALVQQMEQLR,<br>LEPYADQLR   | 330<br>331<br>332<br>333                      | 5.00 | 43788   |
| AF-73  | API-44  | AADDTWEPFASGK  | 334   | 5.21 | 31615   |
| AF-74  | API-45  | GECQAEGVLFFQGDR,<br>YYCFQGNQFLR  | 335<br>336                                    | 6.19 | 51934   |
| AF-74  | API-248 | TIYTPGSTVLYR,<br>TVMVNIENPEGIPVK   | 337<br>338                                    | 6.19 | 51934   |
| AF-75  | API-46  | ELDESLQVAER,<br>EILSVDCSTNNPSQAK   | 339<br>340                                    | 5.03 | 33671   |
| AF-75  | API-225 | LGPLVEQGR,<br>AATVGSLAGQPLQER  | 341<br>342                                    | 5.03 | 33671   |
| AF-121 | API-116 | DNCCILDER,<br>YEASILTHDSSIR,<br>TSTADYAMFK,<br>VAQLEAQCQEPCK,<br>VELEDWNGR,<br>YLQEIYNSNNQK,<br>RLDGSVDFK, | 343<br>344<br>345<br>346<br>347<br>348<br>349 | 5.42 | 105108  |

| AF#    | API#    | Amino Acid Sequences of<br>Trypic Digest Peptides  | SEQ ID<br>NO:   | pI   | MW (Da) |
|--------|---------|--|---|------|---------|
| AF-123 | API-118 | GLIDEVNQDFTNR,<br>ADSGEGDFLAEGGGVR   | 350<br>351  | 7.31 | 64933   |
| AF-124 | API-119 | GLIDEVNQDFTNR,<br>ESSSHHPGIAEFPSR  | 352<br>353  | 7.47 | 64736   |
| AF-125 | API-120 | SGNENGIFYLR  | 354   | 4.77 | 61297   |
| AF-126 | API-121 | DQDGEILLPR,<br>DCQPGLCCAFQR  | 355<br>356  | 4.11 | 60374   |
| AF-126 | API-122 | DQDGEILLPR   | 357   | 4.11 | 60374   |
| AF-127 | API-123 | SLDFTELDVAEEK,<br>ALQDQLVLVAAK   | 358<br>359  | 4.98 | 59649   |
| AF-128 | API-124 | LNMGITDLQGLR,<br>VGDTLNLNLR  | 360<br>361  | 6.60 | 57865   |
| AF-129 | API-125 | KLCMAALK,<br>ELPEHTVK,<br>THLPEVFLSK,<br>HLSLLTTLNLR,<br>FEDCCQEK,<br>LPEATPTLAK,<br>VCSQYAAAYGEK,<br>YTFELSR,<br>LCDNLSTK | 362<br>363<br>364<br>365<br>366<br>367<br>368<br>369<br>370 | 5.29 | 54625   |
| AF-129 | API-126 | SLDFTELDVAEEK,<br>DPTFIPAPIQAK   | 371<br>372  | 5.29 | 54625   |
| AF-130 | API-127 | LQSLFDSPDFSK,<br>LAAAVSNFGYDLYR,<br>TSLEDFYLDEER   | 373<br>374<br>375   | 5.08 | 51880   |
| AF-130 | API-128 | EPGEFALLR,<br>TALASGGVLDASGDYR,<br>VAMHLVCPSR  | 376<br>377<br>378   | 5.08 | 51880   |
| AF-132 | API-130 | DHAVDLIQK,<br>TEQWSTLPPETK,<br>VLSLAQEQVGGSPK,<br>QGSFQGGFR,<br>ADGSYAAWLSR,<br>AEMADQASAWLTR                              | 379<br>380<br>381<br>382<br>383<br>384                      | 4.72 | 47414   |
| AF-133 | API-131 | TQVNTQAEQLR,<br>LEPYADQLR  | 385<br>333  | 5.12 | 44068   |
| AF-134 | API-132 | LEPYADQLR  | 333   | 5.00 | 43516   |
| AF-137 | API-134 | ELDESLQVAER,<br>KYNELLK  | 386<br>387  | 4.98 | 36855   |
| AF-137 | API-135 | AQLGDLPWQVAIK,<br>VFSLQWGEVK   | 388<br>389  | 4.98 | 36855   |

| AF#    | API#    | Amino Acid Sequences of<br>Tryptic Digest Peptides                                      | SEQ ID<br>NO:                          | pI   | MW (Da) |
|--------|---------|---|--|------|---------|
| AF-137 | API-232 | LGPIEAIQK   | 390                                    | 4.98 | 36855   |
| AF-137 | API-233 | LGPLVEQGR,<br>LEEQAQQIR   | 391<br>392                             | 4.98 | 36855   |
| AF-137 | API-234 | KMEENEK   | 393                                    | 4.98 | 36855   |
| AF-139 | API-136 | ELDESLQVAER,<br>IDSLLENDR,<br>EDALNETRESETKLK,<br>EILSVDCSTNNPSQAK,<br>TLLSNLEEAK       | 394<br>395<br>396<br>397<br>398        | 5.00 | 34295   |
| AF-139 | API-137 | SELEEQLTPVAEETR,<br>AATVGSLAGQPLQER   | 399<br>400                             | 5.00 | 34295   |
| AF-140 | API-138 | GLQDEDDGYR,<br>FACYYP   | 401<br>402                             | 6.80 | 32080   |
| AF-141 | API-139 | LLEVPEGR,<br>TNFDNDIALVR  | 403<br>404                             | 7.50 | 28440   |
| AF-142 | API-140 | SNLDEDIIEENIVSR,<br>VELLHNPAFCSLATTK  | 405<br>406                             | 6.75 | 27279   |
| AF-142 | API-141 | LSELIQPLPLER,   | 407                                    | 6.75 | 27279   |
| AF-143 | API-142 | LLIYWASTR,<br>SGTASVVCLLNNFYPR,   | 408<br>409                             | 7.44 | 26066   |
| AF-144 | API-143 | EVDSGNDIYGNPIK,<br>SDGSCAWYR  | 410<br>411                             | 6.56 | 20744   |
| AF-151 | API-145 | AETYEGVYQCTAR,<br>GKPPPSFSWTR,<br>IDGDTIIFSNVQER  | 412<br>413<br>414                      | 5.28 | 137531  |
| AF-153 | API-149 | LNMGITDLQGLR,<br>VGDTLNLNLR   | 415<br>416                             | 9.85 | 69630   |
| AF-157 | API-155 | EPGEFALLR,<br>TALASGGVLDASGDYR,<br>YEAAVPDPR  | 417<br>418<br>419                      | 4.99 | 55449   |
| AF-161 | API-161 | IDQTVEELR,<br>TQVNTQAEQLR,<br>SLAPYAQDTQEK,<br>ALVQQMEQLR,<br>LEPYADQLR,<br>RVEPYGENFNK | 420<br>421<br>422<br>423<br>424<br>425 | 5.18 | 44404   |
| AF-161 | API-162 | TSLEDFYLDEER  | 426                                    | 5.18 | 44404   |
| AF-161 | API-163 | AVFPSIVGR,<br>SYELPDGQVITIGNER,<br>AGFAGDDAPR,<br>GYSFTTTAER,<br>QEYDESGPSIVHR,         | 427<br>428<br>429<br>430<br>431        | 5.18 | 44404   |

| AF#    | API#    | Amino Acid Sequences of<br>Trypic Digest Peptides                  | SEQ ID<br>NO:            | pI   | MW (Da) |
|--------|---------|--|--------------------------|------|---------|
|        |         | VAPEEHPVLLTEAPLNPK   | 432                      |      |         |
| AF-165 | API-168 | EELVYELNPLDHR,<br>EPFLSCCQFAESLR                                   | 433<br>434               | 7.17 | 34230   |
| AF-166 | API-169 | GLCVATPVQLR,<br>EELVYELNPLDHR                                      | 435<br>436               | 8.54 | 33657   |
| AF-167 | API-170 | ASSIIDELFQDR,<br>TLLSNLEEK   | 437<br>438               | 5.69 | 33621   |
| AF-167 | API-171 | GEVQAMLGQSTEELRLAQ,<br>AQQIR,<br>SELEEQLTPVAEETR                   | 439<br>440               | 5.69 | 33621   |
| AF-168 | API-237 | ALEESNYELEGK   | 441                      | 7.66 | 33920   |
| AF-168 | API-172 | GSFEFPVGDAVSK,<br>GLCVATPVQLR,<br>EELVYELNPLDHR,<br>EPFLSCCQFAESLR | 442<br>443<br>444<br>445 | 7.66 | 33920   |
| AF-171 | API-177 | TMLLQPAGSLGSSYSYR,<br>AQGFTEDTIVFLPQTDK                            | 446<br>447               | 4.98 | 29658   |
| AF-171 | API-178 | GSPAINVAVHVFR,<br>AADDTWEPFASGK                                    | 448<br>449               | 4.98 | 29658   |
| AF-179 | API-186 | LIVHNGYCDGR,<br>QEELCLAR,<br>FSGTWYAMAK                            | 450<br>451<br>452        | 5.26 | 20115   |
| AF-180 | API-220 | CSVFYGAPSK,<br>GLQDEDGYR   | 453<br>454               | 6.17 | 16255   |
| AF-182 | API-188 | AADDTWEPFASGK  | 455                      | 4.89 | 13651   |
| AF-185 | API-191 | VGYVSGWGR  | 456                      | 5.32 | 40323   |
| AF-185 | API-192 | SGNENGEFYLR,<br>ADQVCINLR  | 457<br>458               | 5.32 | 40323   |

Table VI

| ERPI#  | ERF#  | Amino Acid Sequences of<br>Tryptic Digest Peptides                    | SEQ ID NO:               |
|--------|-------|---|--------------------------|
| ERPI-1 | ERF-2 | ELLDTVTAPQK,<br>LAAAVSNFGYDLYR,<br>TSLEDFYLDEER,<br>ALYYDLISSPDIHGTYK | 459<br>460<br>461<br>462 |

Table IX. Amino Acid Sequences and Probes for APIs

| AF#    | API#    | Amino Acid Sequences of Tryptic Digest Peptides as Determined by Mass Spectrometry |                              |                       |                       | Preferred Probes (SEQ ID NO) | Degenerate Probes (SEQ ID NO) |
|--------|---------|--|------------------------------|-----------------------|-----------------------|------------------------------|-------------------------------|
|        |         | Mass of singly protonated peptide (Da)*  | Partial sequence (SEQ ID NO) | N-terminal Mass (Da)* | C-terminal Mass (Da)* |                              |                               |
| AF-114 | API-111 | 1097.57  | HQV<br>(463)                 | 0                     | 733.50                | CACCAGGT<br>G (464)          | CAYCARGT<br>N (465)           |
| AF-114 | API-112 | 1547.74  | PGLGM<br>(466)               | 0                     | 1076.63               | CCCGGCCT<br>GGGCATG<br>(467) | CCNGGNYT<br>NGGNATG<br>(468)  |
| AF-114 | API-112 | 1547.74  | PGLGF<br>(469)               | 0                     | 1076.63               | CCCGGCCT<br>GGGCTTC<br>(470) | CCNGGNYT<br>NGGNNTTY<br>(471) |
| AF-114 | API-112 | 1547.74  | PGIGM<br>(472)               | 0                     | 1076.63               | CCCGGCAT<br>CGGCATG<br>(473) | CCNGGNAT<br>HGGNATG<br>(474)  |
| AF-114 | API-112 | 1547.74  | PGIGF<br>(475)               | 0                     | 1076.63               | CCCGGCAT<br>CGGCTTC<br>(476) | CCNGGNAT<br>HGGNNTTY<br>(477) |
| AF-114 | API-112 | 1547.74  | GPLGM<br>(478)               | 0                     | 1076.63               | GGCCCCCT<br>GGGCATG<br>(479) | GGNCCNYT<br>NGGNATG<br>(480)  |
| AF-114 | API-112 | 1547.74  | GPLGF<br>(481)               | 0                     | 1076.63               | GGCCCCCT<br>GGGCTTC<br>(482) | GGNCCNYT<br>NGGNNTTY<br>(483) |
| AF-114 | API-112 | 1547.74  | GPIGM<br>(484)               | 0                     | 1076.63               | GGCCCCAT<br>CGGCATG<br>(485) | GGNCCNAT<br>HGGNATG<br>(486)  |
| AF-114 | API-112 | 1547.74  | GPIGF<br>(487)               | 0                     | 1076.63               | GGCCCCAT<br>CGGCTTC<br>(488) | GGNCCNAT<br>HGGNNTTY<br>(489) |

\*The masses determined by mass spectrometry have an error of mass measurement of 100 parts-per-million (ppm) or less. For a given measured mass, M, having an error of mass measurement of z ppm, the error of mass measurement can be calculated as  $(M \times z \div 1000000)$ .